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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/868,879 | 06/22/2001 | Julian Schofield | 55908(46322) | 9973 |

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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

H/C

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/868,879 | SCHOFIELD ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *46-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

This office action is in response to an amendment filed 12/2/05. Claims 1-45 have been cancelled. Claims 47-67 have been added. Claims 47-67 are pending in the application.

### *Response to Amendment*

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and therefore, this rejection is final.

In the office action mailed 7/2/2004, Bent was referenced inadvertently and has no bearing on this application.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 54 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by applicants' amendment.**

Claim 54 recites the limitation "the liver dysfunction" in claim 51. There is insufficient antecedent basis for this limitation in the claim.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60, 62, 64, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment.**

Applicants recite a method of treating a variety of conditions or diseases that involves administration of GPI-PLD. The invention further recites administration of a genus of variants and fragments of GPI-PLD.

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

In the instant case, applicants disclose the amino acid sequence of human and bovine liver as well as human pancreatic GPI-PLD. Variant and fragments of GPI-PLD that provide the function of full-length GPI-PLD can be used in the methods of treatments. The disclosure teaches that preferred variant GPI-PLD proteins are proteins with substitutions, deletions or insertions at amino acid 713-716 of SEQ ID NO:16. Amino acids 689-692 (or 713-716 of SEQ ID NO:16) comprise a region that is phosphorylated by protein kinase A that switches the

enzyme off. Therefore, it is reasoned that if any of these amino acids are substituted, deleted or receive an insertion of one or more amino acids, the phosphorylation sites is disrupted and the resulting polypeptide has increased activity or half –life (see e.g. page 12, line 1-18). A preferred substitution is serine 692 to any amino acid other than threonine or serine. Preferred fragments of GPI-PLD are GPI-PLD peptides that retain at least in part one of its biological activities e.g. by the presence of a functional N-terminal domain (see page 16, line 32-35). In all cases, the fragments and variants retain or have increased GPI-PLD biological activity especially enzymatic activity in cleaving photodiester bond linking GPI to phosphatidic acid thus releasing GPI anchored proteins (see page 17, line 25-30). Therefore, applicants claim a genus of fragments and a genus of variants with a functional requirement that they retain or have increased GPI-PLD biological activity especially enzymatic activity in cleaving photodiester bond linking GPI to phosphatidic acid thus releasing GPI anchored proteins (see page 17, line 25-30). However, except to define the N-terminal 39kD fragments and the variant that based upon substitution, deletion or insertion at amino acids of 713-716 of SEQ ID NO:16, applicants do not teach the structural requirements for the large genus of potential fragments or variants of any GPI-PLD. Given the large size and diversity of fragments and variants of any GPI-PLD and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species of fragments and one species of variants would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Claims 46-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. **This rejection is maintained for reasons of record in the office action mailed 7/2/04 and restated below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention.** The invention recites a use of glycosylphosphatidyl inositol specific phospholipase D (GPI-PLD) for the preparation of a medicament. The invention utilizes disciplines of protein purification and clinical technology.

2) **Scope of the invention.** The medicament is then used to treat conditions broadly described as those that respond to GPI-PLD or which are characterized by reduced levels of GPI-PLD as compared to a normal patient. Specifically recited conditions are diabetes or diabetic conditions, liver dysfunction or disorders involving pancreatectomies and endotoxin-induced conditions such as septic shock. These steps of therapy exacerbate the complexity of the invention.

3) **Number of working examples and guidance**. The specification teaches that diabetic complications such as insulin resistance *may be caused* by deficiencies in GPI-PLD (see page 5, line 1-11). GPI-PLD is produced by the pancreas and in culture was shown to be secreted in response to insulin secretagogues (page 44, line 33 through page 45, line 4). Applicants describe prior art observations that suggest that the levels of GPI-PLD are responsive to the obese/diabetic genotype as observed in rat streptozotcin-induced diabetes mellitus in which insulin resistance correlated with the impairment of IPG metabolism. As well, mRNA for a GPI-PLD like gene was over-expressed in obese mice (see page 45, line 14-24). Therefore, applicants concluded that GPI-PLD *could* be used as a treatment for diabetes (page 5, lines 6-20). As to the use of GPI-PLD to treat conditions mediated by infectious organisms, it is disclosed that endotoxins are believed to act by inhibiting GPI-PLD. No particular theory as to the mechanism of is provided (see page 8, line 10-15). There is no disclosure as to the association of GPI-PLD and liver dysfunction or pancreatectomies except that patients with liver disease have lower levels of active enzyme, which is correlated with reduced albumin levels (page 45, line 8-12).

The disclosure states that GPI-PLD includes amino acid sequence variants, alleles active portions or fragments (page 15, line 1 through page 18, line 16). The instant inventors have identified a variant, which differs from the amino acid sequence of human GPI-PLD at a phosphorylation site from amino acids 689-692 (see page 16, line 16-21). Other variants are those that are without signal peptide (page 15, line 15-19). Activity of the GPI-PLD is said to reside in the N-terminal 39 kD portion (see page 17, line 35 through page 18, line 1-5). In the working examples, applicants teach the identification and characterization of three clones obtained from human liver libraries- clones a1, b2 and d3. Clone a1 is a full length that differs in

three positions from pancreatic GPI-PLD. Clones b2 and d3 are isoforms of a1. An *in vitro* cell culture system was established from which it was surmised that GPI-PLD is obtained from serum for second messenger signaling.

The specification lacks guidance as to doses or means of administration of GPI-PLD to individuals with the recited conditions. The specifics are left to the responsibility of general practitioners and other medical doctors (see page 24, line 1-20). Instead applicants provide a general review of means of administration and pharmaceutical compositions (page 23, line 1-35).

**State of Art**. GPI-PLD was isolated in the 1980s as a plasma protein. Its characterization continues to date (Rhode et al, page 128, paragraph 4-5). GPI-PLD is relatively new art with incongruous information regarding its *in vivo* functions. Rhodes in addition to several other documents published at the date of filing of the instant invention was interested in correlating GPI-PLD with disease state (see Maguire et al Raymond et al and Rhode et al). In general these references demonstrate that patients with liver disease have lower activity of GPI-PLD than patients with healthy livers. Rhodes et al investigates the possibility that GPI-PLD is contributed from a variety of organs (see page 141, paragraph 3). And more recently, Deeg et al (Am J Physiol Endocrinol Metab 281:E147-E154, 2001) states that the tissue source for circulating GPI-PLD is unknown and whether serum levels are regulated is also unknown (see abstract). However, they do determine that in diabetes GPI-PLD levels are increased. Furthermore, the data is said to be consistent with liver as a contributor to circulating GPI-PLD.

The use of GPI-PLD in medical treatment is a high art with little known. At the time of filing, its use in medicaments was not common. Anderson et al (US 2002/0048576) contemplates

use of GPI-PLD in treating digestive tract infections such as by mycobacterium (see paragraph 0005).

5) **Unpredictability of the art**. The art of protein therapy utilizing GPI-PLD as a therapeutic against conditions that respond to GPI-PLD or are characterized by reduced levels of GPI-PLD such as diabetes, liver dysfunction or endotoxin-induced conditions is highly unpredictable for the following reasons. a) Delivery of biomolecules such as genes and proteins has been a persistent problem for protocols as the route of delivery itself presents an obstacle to be overcome for adequate therapeutic application. Specifically as relates protein therapy, Torchilin and Lukyanov (DDT Vol 8(6):259-266) teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260). Many parameters must be addressed for *in vivo* protein delivery such as lack of toxicity to normal tissues, and the effect of the immune response as well as doses to be administered, dose schedules etc. For example, what level of expression or protein is necessary to achieve therapeutic affects without toxicity to normal cells?

b) The instant invention relies on *in vitro* culture data and observations in the art correlating GPI-PLD to several disease states to formulate an *in vivo* application of GPI-PLD. However, the ability to predict potential success in humans based upon these results is highly unpredictable. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the xenograft and nude mice experimental models and the human

disease state. "Although animal studies have suggested low toxicity and excellent efficacy, these investigation have been limited by the use of immuno-deficient mice" (Meng and Deiry, Gene Therapy of Cancer, 1999, p. 6, column 1). The success of any *in vitro* assays or *in vivo* animal models cannot be considered as evidence of success of treatment, *in vitro* results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies.

6) **Summary**. The invention recites use of GPI-PLD as a medicament for use in conditions that respond to GPI-PLD or are characterized by reduced levels of GPI-PLD as compared to normal patients. The unpredictability of using the claimed invention is accentuated due to the lack of methods or processes disclosed in the instant specification that exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

***Response to Argument***

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph on pages 6-11 of the amendment filed 12/2/04. Applicants' arguments are based upon arguments set forth in a Declaration by Thomas Rademacher filed 12/2/04. The arguments are as follows. 1) The Torchilin and Meng references do not exclude the use of GPI-PLD in the claim methods and

therefore do not support the position set forth in the Office Action. Furthermore, Meng relates to the field of using certain viruses to deliver anti-cancer therapeutics and is therefore not related. 2) Applicants have unpublished data demonstrating that administration of GPI-PLD lowered plasma insulin and raised blood glucose in hyperinsulinaemic and insulin resistant mice (db/db and ob/ob genotype). Applicants argue that the mice are recognized models of human disease and particularly diabetes. The reduction in plasma insulin and increase in blood glucose levels are argued to be indicative of useful therapies. This data is as follows. Enzyme was injected intraperitoneally into ob/ob mice. Insulin levels were measured in plasma. Administration of GLP-PLD reduced blood insulin levels and increased blood glucose. 3) Applicants argue that a worker reading the specification would have known how to administer the GPI-PLD enzyme to treat disease indications.

Applicants' arguments filed 12/2/04 have been fully considered but they are not persuasive. 1) While neither Torchilin nor Meng taught that GPI-PLD therapy is specifically excluded, the teachings were relevant and required to teach what is known in the art regarding therapeutic delivery of biomolecules. Specifically, Torchilin and Lukyanov were applied to the art as it relies on delivery of proteins for treatment of disease or conditions. Torchilin and Lukyanov teach that there are many unresolved problems concerning the delivery of proteins and peptides such as rapid elimination from the circulation through renal filtration, enzymatic degradation, uptake by the reticuloendothelial system and accumulation in non-targeted organs and tissues and inefficient cell entry (see Box 1, page 260). Torchilin and Lukyanov provide valuable insight into the problems of protein therapy. Furthermore, they teach potential means of overcoming these problems. To date, none of these potential solutions have provided the

necessary means to make protein therapy a viable and available means of treating disease. Given the relative paucity of similar reviews based upon protein therapy relative, Meng provides highly relevant teachings related to obstacles for delivery of any biomolecule. For example, Meng and Diery teach that dilution of viruses for example by intravascular or intracavity administration dilutes the vehicle such that only a small portion reaches the relevant site of treatment and that animal studies have suggested low toxicity, and efficacy has been limited by the use of immunodeficient mice. Furthermore, These teachings have been provided to demonstrate that it is well known in the art that the field of therapy based upon biomolecules is in general highly unpredictable.

2) Applicants post-filing data demonstrates a change in glucose and insulin levels in mice for 4 hours. Therefore, applicants post-filing data indicates that two parameters associated with diabetes may be altered transiently in mouse models. It is highly unpredictable based upon the art that the transient change in these two parameters is indicative of treatment. Atkison and Leiter teach that Diabetes in humans is a genetically and clinically heterogonous group of glucose intolerance symptoms (see e.g. page 601, paragraph 1). Gura in a study by the National Cancer Institute has observed that mice did no handle drugs in the same way that humans do. Furthermore, cell culture was not an adequate indicator that the drug would reach its target. Ultimately the mouse model predicts agents that are effective in treating mice but not humans (see Gura, e.g. page 1041, col 1 and col 2, last paragraph). As relates diabetes, Atkinson and Leiter further teach that the mouse model for diabetes has been accompanied by a realization that genus-species differences unavoidably restrict the interpretation of data (see e.g. page 601, last paragraph ). The relevance of NOD mouse model has been likened to that of a single case study,

the etiology of this single case being complex and multifaceted (see page 602, paragraph 1-2). In fact, the real challenge of diabetes treatment is said to be to engineer a system that monitors minute-by-minute changes in glucose levels (see Trivedi, paragraph 2). The post filing data only indicates that upon injection of GPI-PLD, glucose levels can be altered. An adequate therapy would require minute-by-minute analysis of blood glucose levels that are then altered by direct injection of purified protein. As stated above, the means and methods of this treatment are highly unpredictable made more so by the actual lack of treatment of diabetes by GPI-PLD therapy given the multi-faceted and complex nature of diabetes.

3) Given the lack of guidance in the specification, the large and diverse group of disease recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention. A) Neither the specification nor the prior art provides guidance on appropriate means of delivery of purified GPI-PLD protein to a subject or an indication that such therapy has the potential to deliver adequate amount of protein to a subject that is not cleared by normal or allergic responses. b) Applicants have recited a large and diverse group of conditions. These conditions are said to be those that responsive to GPI-PLD or are characterized by low levels of GPI-PLD as compared to normal patients. The art reviewed above indicates that patients with liver disease have lower activity of GPI-PLD. Deeg et al have taught that GPI-PLD is elevated in diabetic mice. Specifically, applicants have recited for treatment diabetes or diabetic conditions, liver dysfunction or disorders involving pancreatectomies and endotoxin-induced conditions such as septic shock. The art of treatment of diabetes alone is complicated and to date no response to a single agents has been effective. For any other of the recited disorders, it is highly unpredictable

that administration of GPI-PLD will *treat* all of these conditions. c) Means of administration as described by Meng and Torchilin are persistent problems for therapy based upon biomolecules. d) Current therapeutic relevance of *in vivo* and *in vitro* data is highly unpredictable.

***Conclusion***

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 6, 2004

GERRY LEFFERS
PRIMARY EXAMINER